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Stimulating the Aberrant Brain: Evidence for Increased Cortical Hyperexcitability
from a transcranial Direct Current Stimulation (tDCS) study of Individuals
Predisposed to Anomalous Perceptions.

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Abstract

Findings from neurological and clinical groups have shown that increased predisposition to anomalous experience / aura reflects an elevation in aberrant neural processes in the brain. However, studies of anomalous experiences in non-clinical / non neurological groups are less clear on this matter and are more typically confined to subjective questionnaire measures alone. The current investigation, the first to our knowledge, carried out a transcranial Direct Current Stimulation (tDCS) study of cortical hyperexcitability, and its association with anomalous experience in non-clinical / non neurological groups. Sixty participants completed; (i) both excitatory (anodal) and inhibitory (cathodal) brain stimulation conditions of the visual cortex; (ii) a computerised pattern-glare task, where observers reported phantom visual distortions from viewing highly irritable visual patterns (a metric of cortical hyperexcitability), and; (iii) questionnaire measures of predisposition to anomalous perceptions. There were no reliable signs of cortical hyperexcitability (via pattern-glare tasks) when collapsed across the whole sample. However, a significant positive correlation between predisposition to anomalous experience and elevated signs of cortical hyperexcitability was observed. Crucially, there was a significant negative correlation between tDCS stimulatory conditions. A visual cortex that reacted more strongly to excitatory stimulation, responded less well to inhibitory suppression, and this pattern was related to predisposition to anomalous perceptions. Both findings are consistent with the presence of a hyperexcitable cortex. Collectively the present findings provide objective evidence that the brains of individuals predisposed to anomalous experiences / hallucinations can be hyperexcitable - even in the non-clinical / non-neurological population. These data are consistent with continuum models of anomalous experience and have important implications for contemporary theories of aberrations in self-consciousness.

Anomalous visual experience, including visual distortions, visual hallucination, and aura, are known to be tractable to aberrant neurophysiological activity and an increased degree of cortical hyperexcitability (Aleman & Larøi, 2008; Allen, Larøi, McGuire, & Aleman, 2008; Bien et al., 2000; Braun, Dumont, Duval, Hamel-Hébert, & Godbout, 2003; Bressloff, Cowan, Golubitsky, Thomas, & Weiner, 2001; 2002; Gloor, 1986; Manford and Andermann, 1998; Panayiotopoulos, 1994; 1999; Siegel, 1977; Taylor, Scheffer, & Berkovic, 2003).

This is evidenced, at least in part, by a variety of neurological disorders and psychopathologies where, without exception, aberrations in underlying neurophysiological activity and anomalous experiences are known to be co-present. This includes (though is not restricted to); migraine with aura, occipital migraine, epilepsy, migralepsy, visual stress, Charles-Bonnet syndrome; schizophrenia, schizotypy, psychoses, depersonalization / derealization, and various dissociative disorders (Allen et al., 2008; Bien et al., 2000; Braun et al., 2003; Feinberg & Keenan, 2005; ffytche & Howard, 1999; ffytche et al., 1998; Manford & Andermann, 1998; Sierra, 2009). As a consequence, the presence, intensity and frequency of anomalous experiences may well be indicative of both a general underlying increase in cortical hyperexcitability (present and quantifiable inter-ictally) and transient paroxysmal neural activity. Put simply, the anomalous mind is, what the aberrant brain does.

In addition, both studies of electric and magnetic brain stimulation have shown that hallucinatory experiences can be more effectively induced in those known to have more labile brains (neural vulnerabilities indicating a less inhibited, more excitable cortex: Aurora, Ahmed, Welch, Bhardhwaj, & Ramadan, 1998; Aurora, Welch, & Al-Sayed, 2003; Halgren, Walter, Cherlow, & Crandall, 1978; Penfield & Perot, 1963; Young, Young et al., 2004; Wassermann, 1998). Collectively, the emerging picture is one where the elevated presence of anomalous experience appears to reliably reflect increased cortical hyperexcitability. Furthermore, that excessive neural excitation can significantly impact on the phenomenological contents of ongoing conscious experience. Similar observations have been reported in the nonclinical population where

elevated signs of neural dysfunction (in the form of brief paroxysmal activity) have been shown to be associated with the predisposition to report paranormal / spiritual experiences (Makarec & Persinger, 1987, 1990; Neppe, 1983; Persinger, 2001; Persinger & Koren, 2001; Persinger & Makarec, 1986, 1993). These findings lend support to the *continuum* hypothesis, where individuals can be placed along a dimension of neural instability / cortical hyperexcitability with the implication being that such factors are not the exclusive domain of pathological conditions and disorders. Although the notion of a continuum of hallucination proneness is well founded, with few exceptions most demonstrations of increased neural instability are confined to indirect questionnaire measures of predisposition to anomalous experiences.

Quantifying Cortical Hyperexcitability

Behavioural tasks have been used to assess cortical hyperexcitability in a variety of patient groups. For example, meta-contrast masking effects have been shown to be reduced for migraineurs with aura, relative to migraineurs without aura and control groups (Palmer, Chronicle, Rolan, & Mulleners, 2000). Palmer and colleagues argued that these findings evidence a reduced role of GABA mediated lateral inhibition in the primary visual cortex of migraineurs with aura. The idea that a hyperexcitable cortex does indeed underlie the presence of anomalous perceptions / aura has been furnished by studies showing; (i) that the threshold at which phosphenes are induced (via Transcranial Magnetic Stimulation: TMS of the visual cortex) is significantly reduced in migraine patients with aura; and that; (ii) the visual cortex of migraineurs with aura also produces visually-evoked potentials of a higher amplitude, which also fail to habituate, relative to non-aura migraineurs and controls (Aurora & Welch, 2000; Aurora & Wilkinson, 2007; Aurora, Cao, Bowyer, & Welch, 1999; Aurora et al., 1998; Aggugia, Zibetti, Febbraro, & Mutani, 1999; Gawel, Connolly, & Rose, 1983; Young et al., 2004). Such observations suggest that the visual cortex is indeed hyperexcitable, inter-ictally, in migraineurs, but only those who report aura / visual hallucinations.

Aberrant cortical hyperexcitability has also been explored through tasks that use irritable visual stimuli which, it is argued, over-stimulate localised neural assemblies in visual association cortex. For example, viewing square-wave striped gratings with a spatial frequency of approximately 3 cycles-per-degree (cpd) of visual angle can be highly irritable to observers, inducing visual discomfort and a host of phantom visual distortions – a phenomenon termed ‘*pattern-glare*’ (Wilkins, 1995, 1986, Wilkins et al., 1984; Evans & Drasdo, 1991; see Evans & Stevenson, 2008; for a review). The distortions can vary but include; illusions of colour (halos), shadows, shimmer, flicker, and motion. These stimuli are known to be highly epileptogenic, are a potent trigger of seizures and attacks in specific populations (i.e., photosensitive epilepsy) and are visually aversive to view.

Increased pattern-glare has been shown to be particularly prominent in those with migraine with aura (Friedman & De ver Dye, 2009; Harle & Evans, 2004; Marcus & Soso, 1989), visual stress (Evans, Busby, Jeanes, & Wilkins, 1995; Evans & Stevenson, 2008), photosensitive epilepsy and stroke (Beasley & Davies, 2012; Evans, 2005; Evans & Stevenson, 2008) and certain hallucinations in the non-clinical population (Braithwaite, Broglio, Bagshaw, & Wilkins, 2013a; Braithwaite, et al., 2013b). It has also been implicated in cases of anxiety / mood disorders and its severity can vary in sympathy with the presence of other co-morbid factors (see Ludlow, Wilkins, & Heaton, 2006; Nulty, Wilkins, & Williams, 1987; Wilkins, 1986).

Findings from neuroscientific investigations (i.e., brain-imaging) provide more direct evidence that stripe-induced visual discomfort and distortions reflect hyperexcitability mediated at the cortical level. For example, using fMRI Huang and colleagues showed an increased BOLD response in visual association cortex, but only in migraineurs with aura and only for the medium-frequency grating (Huang et al., 2011). In addition, the degree of pattern-glare reported by observers correlated with the level of neural activity in visual and visual association cortex (Wilkins, Tang, Irabor, Baningham, & Coutts, 2008), and the time course for the cortical response (examined via Near-Infrared-Spectroscopy) from migraine with aura patients was reduced relative

to controls - but again, only for the medium frequency grating (consistent with a more reactive cortex in these patient groups: Coutts, Cooper, Elwell, & Wilkins, 2012). Therefore, both an aberrant level of response and more reactivity in the timing of it, index a hyperexcitable cortex. As a consequence, the notion of a relationship between the presence of perceptual aberrations / hallucinations and cortical hyperexcitability has broad empirical support from behavioural and brain-imaging investigations with neurological and clinical groups.

Transcranial Direct Current Stimulation (tDCS):

Transcranial direct current stimulation (tDCS) is a non-invasive technique of electrical brain stimulation, which has been shown to modulate baseline cortical activity in humans (see Nitsche et al., 2008, for a review). As a method, tDCS allows for the exploration of sustained changes in background cortical hyperexcitability. Growing evidence suggests that the application of tDCS can modulate cortical excitability, leading to modifications in cognitive and behavioural functions in both neurological samples and the non-clinical population. (Antal, Kincses, Nitsche, & Paulus, 2003; Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004; Antal, Terney, Poreisz, & Paulus, 2007; Nitsche et al., 2008; Antal, Paulus, & Nitsche, 2011; Jacobson, Koslowsky, & Lavidor, 2012; Nitsche & Paulus, 2011; Vallar & Bolognini, 2011). tDCS effects have now also been shown to occur in a number of cortical regions including visual cortex (Antal et al., 2004).

For example, the application of tDCS has been shown to influence the amplitudes of Visual Evoked Potentials (VEPs) where anodal (excitatory) tDCS increased occipital responses and cathodal (inhibitory) tDCS attenuated them (Antal et al., 2004; see also Accornero, Voti, La Riccia, & Gregori, 2007). Ten minutes of anodal tDCS over occipital cortex has also been shown to modulate phosphene thresholds (PTs) that were subsequently induced by Transcranial Magnetic Stimulation (Antal et al., 2004). This reduction in PT is taken as an indicator of increased cortical excitability, which is taken to mimic endogenous hyperexcitability in certain groups.

Stronger effects of tDCS on phosphene thresholds have also been demonstrated for migraine-with-aura patients - consistent with the notion that these patients have a hyperexcitable visual cortex which underlies the existence of anomalous perceptions, distortions, and hallucination (Chadaide, Arlt, Antal, Nitsche, Lang, & Paulus, 2007). In this study, Chadaide et al., (2007) found that the largest reduction in PT was observed for migraineurs with aura relative to migraineurs without aura and non-migraine controls. More specifically, excitatory anodal stimulation induced an increase in cortical excitability, which was largest in aura participants. Inhibitory cathodal stimulation had no reliable effect on the migraine groups (but did on controls). These findings lend support to the view that deficient inhibitory processes (leading to a hyperexcitable cortex) are directly associated with the occurrence of visual aura / hallucinations in some patient groups.

Although numerous demonstrations of the efficacy of tDCS have now been reported, the underlying biophysics of tDCS are still somewhat unclear. It is generally thought that tDCS exerts its effects by modifying spontaneous neuronal activity via shifting the resting membrane potential in a polarity-dependent manner. By this account, anodal (excitatory) stimulation induces an increase in the background spontaneous firing rate by depolarizing cell membranes. In contrast, cathodal (inhibitory) stimulation attenuates cortical excitability by hyperpolarizing cell membranes (Romero-Lauro et al., 2014). When coupled to the findings from those prone to visual aura / hallucination, the implication is that transient paroxysmal neural firing becomes more likely and may ride on the back of these more gradual changes in membrane potential. Thus, as membrane potentials gradually approach depolarization thresholds as a background state in the neural microenvironment under anodal stimulation, aberrant neurophysiological processes of the type known to be associated with hallucinations become more likely.

It is also important to note that the effects of tDCS have been argued to be somewhat diffuse and not as spatially focused as those from other methods (i.e., trans-cranial magnetic stimulation: Romero-Lauro et al., 2014). The stimulatory effects of tDCS are thought to occur not only in the regions directly beneath or immediately proximal to the electrodes, but they also permeate through

brain tissue - suggesting both localised and more general stimulatory effects (Miranda, Mekonnen, Salvador, & Ruffini, 2013; Romero-Lauro et al., 2014). Therefore, although one may place an electrode over primary visual cortex, the diffuse effects of tDCS may also propagate into spatially distant visual association cortex and the regions defined by both electrodes (Keeser et al., 2011; Peña-Gómez et al., 2012).

Overview of the current study

The present study sought to examine the role of cortical hyperexcitability in relation to the predisposition to anomalous and hallucinatory perceptions in the non-clinical population. If anomalous perceptions are associated with aberrant and elevated neurophysiological activity, then individuals displaying an increased predisposition to such experiences may also display signs of cortical hyperexcitability. To the best of our knowledge the current study is the first to examine tDCS on the effects from pattern-glare, as an index of cortical hyperexcitability in those prone to non-clinical levels of anomalous perceptions / hallucinations.

Elevated levels of pattern-glare have been shown previously to be associated with some multi-sensory hallucinations (i.e., the out-of-body experience) that contain a strong visual component (Braithwaite et al., 2013a, 2013b) - suggesting that such hallucinations are associated with a hyperexcitable cortex even in non-neurological / clinical populations. However, these previous studies were based on behavioural data alone. The present investigation sought to explore this premise with more objective direct brain-stimulation manipulations. In addition the present study also sought to investigate both the excitatory and inhibitory effects of tDCS on brain function. Based on previous findings (discussed above) we hypothesised that an asymmetrical effect may occur where a hyperexcitable cortex that reacts more strongly to excitatory stimulation, may also be less responsive to inhibitory suppression of the cortex and that such a pattern is further associated with predisposition to anomalous and aberrant experience.

To examine these issues, a modified computer-based version of the pattern-glare test was devised (see Braithwaite et al., 2013a, 2013b). As discussed in the Introduction, it is now known that increased signs of pattern-glare reflect stronger neuronal responses to irritative gratings - cortical hyperexcitability (Coutts et al., 2012; Huang et al., 2011; Wilkins et al., 2008). The task provides a measure of the degree of latent cortical hyperexcitability at the specific time of testing. Coupled to this, participants also completed the Cardiff Anomalous Perception Scale (CAPS: Bell, Halligan, & Ellis, 2006) as a more general measure of individual predisposition to experience anomalous perceptions. Previous studies from our laboratory have shown that the "Temporal-lobe Experience" factor from the CAPS can reliably delineate those prone to anomalous-body experiences including the out-of-body experience in non-clinical / non-neurological groups (Braithwaite, Brogna, & Watson, 2014; Braithwaite et al., 2013a, 2013b; Braithwaite, Hulleman, Samson, & Apperly, 2011). It is important to note that although the factor is termed a temporal lobe one, in reality the experiences contained on it include a variety of visual and multisensory experiences which likely reflect aberrant processes from a variety of cortical and sub-cortical regions. These items reflect experiences that are commonly reported in pre-seizure aura-type experiences by patients with occipital and temporal-lobe epilepsy and in patients undergoing direct electrical stimulation as part of surgery (Gloor, 1986; Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982; Halgren et al., 1978; Penfield, 1955; Penfield & Perot, 1963) as well as those reported by the non-clinical population (Makarec & Persinger, 1987, 1990; Persinger & Makarec, 1986, 1993; Persinger, 2001).

Method

Participants

Sixty-one healthy volunteers (all female and all right-handed; mean age: 19.8 years, age range: 18-29 years) took part in the study for course credit or a small financial reward. Only female participants were used in order to control for gender differences but also due to a higher precedence

for hallucination in female groups relative to males. Participants were undergraduate or postgraduate students recruited via the Research Participation Scheme at the School of Psychology, University of Birmingham, UK. Participants were not eligible to take part if they had previously participated in a tDCS or TMS study within the preceding 6 months before this study. All participants had no known visual impairments, neurological disorders or had taken psychiatric medication. Additional exclusion criteria included a medical history of migraine (with or without aura), photosensitive epilepsy, temporal-lobe epilepsy, and / or seizures of unknown origin. Participants, were also asked to abstain from alcohol the night before an experimental session and from coffee two hours prior to any given session. The study was approved by the Ethics Committee of the University of Birmingham [ERN_12-0466].

Questionnaire measure

The Cardiff Anomalous Perceptions Scale (CAPS)

The CAPS is a parametrically validated measure consisting of 32-items pertaining to predisposition to perceptual anomalies across a range of senses (Bell et al., 2006). Participants were asked to respond to each question with a 'yes' / 'no' (scored '1' / '0' respectively). In the original CAPS measure, a subscale of 11-items (Questions 1, 2, 4, 6, 10, 12, 16, 24, 26, 27, 32) were defined as a "Temporal-Lobe Experience Factor", reflecting anomalous experiences associated with temporal lobe dysfunction (Bell et al., 2006; see also Bell, Halligan, Pugh, & Freeman, 2011). The TLE factor has been shown to reliably delineate those prone to multisensory out-of-body experiences and other related anomalous body experiences in the non-clinical population (Braithwaite et al., 2013a, 2013b, 2011).

The Pattern-glare task

The present experiment employed a modified version of the computerised pattern-glare task as devised for previous investigations (Braithwaite et al., 2013a, 2013b). The experiment was carried out in a dimly lit laboratory where the computer monitor was the main source of illumination. The experiment was programmed in E-prime version 2.2. The pattern-glare stimuli consisted of three separate achromatic square-wave gratings that differed only in terms of their spatial frequency (SF). The three separate spatial frequencies were; (i) a low spatial-frequency baseline grating of approximately 0.5 cycles-per-degree (cpd); (ii) a high spatial-frequency baseline grating (approximately 14.0 cpd), and (iii) the critical medium spatial-frequency grating (approximately 3.4 cpd)¹. In addition to these gratings, a non-irritating checkerboard stimulus (approx. 0.5 cpd both horizontally and vertically) was used as filler stimuli, with the aim of breaking up the potentially irritating effects of the gratings and preventing habituation, which might occur due to the repetitive presentation of horizontal gratings only. All stimuli had a Michelson contrast set at 0.75 (10 cd/m²). The mean luminance of the gratings was 40 cd/m². The screen background (grey 50%) luminance was 20 cd/m².

All stimuli were presented separately and centrally on a high resolution display monitor (20-inch CRT screen, Hewlett-Packard®, HP-p1230 monitor with a 1600 × 1200 pixel resolution and an 85Hz refresh rate). The stimuli size extended over an area of 110mm wide by 115mm high, which translated into a visual angle of 7.87 × 8.22 degrees, from the viewing distance of 80 cm. The presentation of the stimuli was determined in a pseudo-random order with the only restriction being that the same grating was not presented twice in a row.

Each trial began with the presentation of a small square fixation point on the screen for 8 seconds. After this period, a stimulus was presented (a grating or a filler stimuli, the fixation point remained present in the middle of the stimulus). Participants were instructed to concentrate on the

¹ Wilkins et al (1984) examined the irritable effects of a range of frequencies and although a frequency of between 2 - 4 cpd was maximally irritating, gratings with a density up to 8 cpd also produced significant discomfort. Therefore, the high-frequency grating needs to be sufficiently above those values to ensure one does not unintentionally use an irritable grating as a baseline, thus abolishing any chance of a pattern-glare effect.

fixation point until the fixed stimulus presentation time of 12 seconds had passed. Participants were instructed that if the stimulus was too uncomfortable to look at during this phase, then pressing the spacebar would remove the grating from view. A further pressing of the space-bar would make it reappear and so on. The numbers of space-bar presses were also recorded for each and every stimulus as an additional measure of visual discomfort.

The end of the viewing period was signalled by the presentation of a list of associated visual or visually induced distortions (AVDs) on screen, which included distortions like; shimmering, flickering, blur, shadows, bending of lines, nausea, pain, coloured halos (red, green, yellow, blue); see Braithwaite et al., 2013a, 2013b). Participants were instructed to click on as many or few AVDs to represent what they experienced during the 12-second viewing time before clicking on the option to continue to the next screen. At the end of each trial, participants were asked whether the AVDs experienced occurred in the left visual field (LVF), right visual field (RVF), both visual fields equally, or neither visual field. On completion, an inter-stimulus interval of 8 seconds was presented where all stimuli were cleared from the screen and this procedure repeated itself until the end of the block and all trials had been completed. Each stimulus type was presented three times within the block of trials. The block was completed twice (24 trials in total) with a short break between the blocks to relieve the visual system.

Transcranial Direct Current Stimulation (tDCS stimulation)

tDCS was delivered by a battery-driven direct current stimulator (Magstim Ltd., UK) via a pair of conductive rubber surface electrodes ($5 \times 5 \text{ cm}$, area = 25 cm^2 , one for anode and another for cathode). The electrodes were housed in sponges soaked with a saline solution of sodium chloride (1.8 % NaCl). It has been recently shown that different sized electrodes might have a more (or less) specific effect over the stimulated sites (Nitsche et al. 2007). However, it is not clear whether utilising such a montage is beneficial in all cases and over all combinations of target and reference

cites. We have therefore opted to use such montages that have been shown to have an excitatory/inhibitory effect over visual cortex (e.g., Chadaide et al., 2007).

To excite visual cortex, one of the electrodes was placed over the cortical location Oz and the other (reference) was placed over Cz (vertex), in accordance with the International 10/20 electrode positioning system (Antal, Nitsche, & Paulus, 2006; Antal & Paulus, 2008; Nitsche et al., 2008). We measured individual cortical size and determined the appropriate electrode locations. For anodal stimulation (excitatory configuration / increasing neuronal excitability) of the visual cortex, the anode electrode was placed over Oz and the cathode electrode was placed over Cz. For cathodal stimulation (inhibitory configuration / decreasing neuronal excitability) of the visual cortex, the positions of the electrodes were reversed.

The stimulation parameters (current intensity and duration) were chosen in accordance with the safety criteria, for preventing any side-effects caused by cortical excitability modulation (Nitsche et al., 2003; Nitsche et al., 2008; Poreisz et al., 2007), and were commonly used in previous experiments for exploring visual cortex functions (e.g. Antal et al., 2004, Spiegel, Byblow, Hess, & Thompson, 2013, Spiegel, Hansen, Byblow, & Thompson, 2012, Viganò et al., 2013). The stimulation intensity and duration were at the upper ends of tDCS protocols in order to ensure, as much as possible, that effects of tDCS would not be offset by the effects of presenting the potent gratings themselves. As already noted, pattern-glare effects arise because the presentation of the medium-frequency grating over-stimulates neurons in visual cortex and this aberrant activity likely underlies the perception of the resultant visual distortions reported. Therefore, even under sham conditions, one is still effectively stimulating the visual cortex to some degree (visually) with highly potent visual stimuli. The battery-driven simulator was programmed to deliver the constant DC current intensity for the stimulus duration with a linear fade-in of 30 seconds at the start of the stimulation period and a linear fade-out of 30 seconds at the end of stimulation period, in order to avoid alternating current causing transient neuronal firing. For each active stimulation (anodal and cathodal condition), the tDCS was applied for 20 minutes durations with an intensity of 1.5 mA on

a 25cm² electrode surface area, thus the current density was approximately 0.06 mA/cm² through the DC-stimulator (During the experiment, the electrical resistance was monitored by the experimenter as being held constant below 5kΩ.)². A schematic overview of the stimulation procedure and experimental protocol is given in Figure 1.

 Insert Figure 1 here

In the sham condition, the electrode arrangements were identical to the active (both anodal and cathodal) condition. The stimulation was maintained for only the first 30 seconds duration to mimic similar initial cutaneous sensations (e.g. itching) participants might experience during the real condition. By termination of the stimulation after 30 seconds, any effects induced by tDCS were prevented (Nitsche et al., 2008).

All participants were administrated all three tDCS conditions: anodal, cathodal, and sham (within-subjects design). The order of three tDCS sessions was randomly assigned for each participant and followed the identical testing protocols. All participants took part in sessions that occurred a minimum of every other day (i.e., Monday, Wednesday, Friday)³.

Experimental Procedures

At the first session, the participants completed measures of predisposition to anomalous perceptions (the CAPS: Bell et al., 2006), which was presented electronically (programmed in Microsoft Access) on a laptop computer. The participant also completed tDCS safety questionnaires. All

² Note - these stimulation parameters are, on the whole, slightly higher than those of Nitsche et al (2008).

³ The actual order (out of six possible combinations of stimulation order) was treated as a between-subjects factor and separate one-way ANOVAs were carried out on the three separate stimulation conditions. Importantly, there were no reliable effects of the order in which the sessions were done on the number of AVDs reported from any condition (Excite condition, $F(5, 54) = .586$, $p=.710$; Inhibit condition, $F(5, 54) = .678$, $p=.642$, and Sham, $F(5, 54) = 1.45$, $p=.218$).

reported that they were not taking any drugs (excluding contraceptive pills), caffeine and alcohol prior to the experiment. The participant's head size was measured and then the suitable stimulation positions were confirmed. The tDCS electrodes were then placed on the scalp. The tDCS device was located out of participants' sight at all times. Participants were blinded as to which tDCS conditions they were taking part in (excitation / inhibition / sham).

All Participants were provided with instructions for the pattern-glare task and taken through definitions for the AVDs. After the 10 minutes of initial tDCS stimulation, a short practice block with low-frequency checkerboard stimuli (so as to be non-irritable and so that they could familiarise themselves with the procedure) was undertaken. tDCS stimulation continued through the pattern-glare task - with the total stimulation time being 20mins. Each experimental session lasted approximately 40 minutes in total (including questionnaires and exit briefing). After completion of all three sessions, participants were asked which of the sessions were the active stimulation ones and which one was sham stimulation. Their guessing was a chance level.

Different data sets were analysed via a combination of parametric and non-parametric statistics (i.e., Spearman rho, ANOVA, t-tests). For stimulation conditions, the data were made fit for analysis by producing a series of subtractions (creating a series of delta values) relative to the sham condition (explained more fully in the Results section below). All reported statistical p-values are two-tailed.

Results

One participant was removed from the analysis for an excessively high number of AVDs for the low-frequency baseline grating (more than 50% of the theoretical maximum for the grating). The analysis was carried out on the remaining 60 participants. The overall number of AVDs reported for the low-frequency grating were extremely low for the remaining sample ($\bar{X} = 0.85$).

As this grating is really only used as an index of suggestibility, and the number of AVDs was very low, in line with previous research we discarded the AVD data from the low-frequency grating from further analysis. Predisposition to anomalous perceptions was provided by scores on the CAPS measure and the TLE factor subscale from the CAPS. Overall descriptive statistics for both the CAPS and the 11-item TLE factor measure of proneness to anomalous perceptions, are given in Table 1⁴.

 Insert Table 1 here

A Shapiro-Wilks test was conducted on both overall CAPS and TLE scores, and revealed a non-normal distribution for both components, ($W=0.90$, $p<.001$, and $W=0.93$, $p<.005$), respectively. Therefore, the correlation between these factors and ratings on the pattern-glare task were explored via a non-parametric Spearman's rho statistics.

To provide a measure of the overall degree of cortical hyperexcitability in participants, irrespective of stimulation, both the CAPS and TLE measures were correlated with the mean number of AVDs reported from the sham (non-stimulatory) condition of the pattern glare task. AVDs were counted and then divided by the number of trials for that grating (i.e., 6 in the present case) to gain a mean average measure of AVDs for each grating, and for each individual. Only the correlations involving the medium-frequency grating were reliable, CAPS x medium-frequency AVDs, ($\rho = 0.33$, $n=60$, $p<.01$); and TLE x medium-frequency AVDs, ($\rho = 0.48$, $n=60$, $p<.001$). Neither measures of proneness to anomalous experience correlated significantly with the number of AVDs reported for the high-frequency grating (all $\rho < .13$; all $P_s > .32$).

⁴ Note, to ensure independence in the measures, the CAPS statistics are based on the remaining 21 items after the 11 TLE items have been removed and analysed separately.

These findings support previous research (Braithwaite et al., 2013a, 2013b) and suggest that the propensity to experience more AVDs in response to the presentation of the medium-frequency grating, is associated with propensity to experience certain anomalous perceptions. In addition, although both correlations were significant, they were stronger for the TLE factor than the remaining questions from the CAPS measure suggesting that the items on the TLE scale are more strongly associated with the mechanisms underlying predisposition to experience increased AVDs.

Effects of pattern-glare

No participant found the gratings so uncomfortable as to remove them from the screen (via pressing the spacebar). Therefore, spacebar presses, as a potential measure of excessive visual discomfort, could not be analysed further. In addition, all participants reported that AVDs were experienced either equally in both visual fields, or there was 'no effect'. Similarly, these visual field effects were not analysed further. The mean number of AVDs for the medium-frequency and high-frequency gratings were analysed via a within-subjects t-test on the whole sample. Although there was a trend for more AVDs to be reported for the medium-frequency grating ($\bar{X} = 3.21$), relative to the high-frequency grating ($\bar{X} = 2.91$), this trend failed to be reliable under sham (no stimulation) conditions, ($t = 1.63$, $df = 59$, $p = .110$).

Effects of brain stimulation using tDCS

Effects of stimulation were initially explored via a 2 (Gratings: Medium / High) x 3 (Stimulation: Sham / Inhibition / Excitation) within-subjects ANOVA carried out on the entire sample. Both the main effects of Grating, $F(1, 59) = 11.74$, $p < .001$, and the main effect of Stimulation, $F(2, 118) =$

24.20, $p < .001$, were significant,. The Grating x Stimulation interaction was also significant, $F(2, 118) = 27.84$, $p < .01$ (see Figure 2).

 Insert Figure 2 here.

The interaction was explored further by carrying out a one-way ANOVA on each grating separately, across the three stimulation conditions. This revealed no effect for the high-frequency grating, $F(2, 118) = .700$, $p = .499$. On the whole, tDCS stimulation had little effect on the number of AVDs reported for the high-frequency grating. In contrast, there was a significant effect for the number of AVDs reported for the medium-frequency grating across the stimulation conditions, $F(2, 118) = 75.65$, $p < .001$.

Individual within-subjects t-tests, revealed that there were significantly more AVDs reported in the excitatory condition, relative to the sham condition, ($t = 7.86$, $df = 59$, $p < .001$). To a lesser extent, there were also fewer AVDs in the inhibitory condition, relative to the sham conditions, ($t = 3.10$, $df = 59$, $p < .02$). The difference between excitatory and inhibitory conditions was also reliable, ($t = 10.52$, $df = 59$, $p < .001$), with excitatory conditions being associated with significantly more AVDs. Overall, it appeared as if the number of AVDs was influenced by both excitatory, and to a much smaller extent, inhibitory configurations of tDCS (relative to a sham condition). Finally, the difference between the number of AVDs for each grating, in each stimulation condition, was examined. Relative to the high-frequency baseline grating, the number of AVDs for the medium-frequency grating were significantly increased under excitatory configurations of tDCS, ($t = 5.63$, $df = 59$, $p < .001$). However, there were no reliable differences between the number of AVDs under sham, ($t = 1.62$, $df = 59$, $p = .110$), or inhibitory conditions, ($t = 1.58$, $df = 59$, $p = .119$).

To explore the impact of tDCS further, we took the mean number of AVDs from the tDCS excitation condition, and from these, subtracted the mean number of AVDs from the sham condition. This essentially generated a 'delta' score, for each individual. Based on the reasonable assumption that excitatory stimulation of the visual cortex should produce more AVDs, this gave us a delta-metric of any increases in AVDs from excitatory brain stimulation relative to a sham baseline condition for the same stimulus. In addition, we then took the mean number of AVDs from the sham condition, and from them, subtracted the AVDs from the inhibitory stimulation condition. This gave us a delta-metric of any suppression in AVDs from inhibitory tDCS brain stimulation. We did these calculations for both the medium-frequency grating and the high-frequency baseline grating.

For each grating type (medium / high) the effects of excitation were then correlated with the effects of inhibition. For the medium-frequency grating, this revealed a significant negative correlation ($\rho = -0.48$, $n=60$, $p<.001$: see Figure 3). The greater the increase in AVDs reported due to excitatory tDCS stimulation, the less effective inhibitory configurations of tDCS were at suppressing AVDs (less difference between sham and inhibition). In contrast, although a similar negative trend occurred for the same analysis for high-frequency baseline gratings, the coefficient was less than half in magnitude and failed to be reliable, ($\rho = -0.22$, $n=60$, $p=.08$).

Insert Figure 3 here

As significant effects only emerged for the medium-frequency grating, the relationship between propensity to experience anomalous perceptions and cortical hyperexcitability was explored further

by correlating the subtraction delta scores outlined above with both the CAPS and TLE measures (see Table2).

Insert Table 2 here

As Table 2 shows, only the deltas for the excite - sham condition produced a significant correlation and only for scores on the TLE factor. There were no correlations involving the inhibition stimulation conditions.

General Discussion

The present study investigated quantitative effects of cortical hyperexcitability on individuals predisposed to aberrant visual experience. The number of visual distortions that occurred from viewing aversive gratings under sham (non-stimulatory) conditions and conditions of tDCS brain stimulation were examined. These factors were also explored in relation to the propensity to report anomalous perceptual experiences which arguably reflect a habitual or latent degree of aberrant neural activity.

It was hypothesised that if certain anomalous perceptions and hallucinations do reflect, at least in part, a hyperexcitable visual cortex then those prone to such experiences might also display; (i) increased numbers of visual distortions associated with viewing aversive patterns; and (ii) that their hyperexcitable brain might react more easily to excitatory brain stimulation using tDCS over visual cortex. Both findings would support the notion that the pattern-glare task is a reliable

indicator of centrally mediated aberrant cortical processes and can reveal an important underlying concomitant of aberrant experience in certain people.

In terms of the overall mean number of AVDs reported by the sample under sham conditions, there were no reliable effects of pattern-glare. Although there was a small trend for more AVDs to be noted when viewing the medium-frequency grating, relative to the high-frequency grating, roughly equal numbers of AVDs were reported for both gratings. This suggests that the current sample, as a whole, did not display strong effects of cortical hyperexcitability as a background latent variable (which is to be expected as pattern-glare is associated with aberrant neural processes which should not be overly prevalent in the general population).

However, the number of AVDs for the medium-frequency grating did correlate significantly with questionnaire measures of predisposition of anomalous experience. The correlation was moderately stronger for the TLE x AVD comparison ($\rho = 0.48$) than for the CAPS x AVD comparison ($\rho = 0.33$) suggesting that the experiences represented by the TLE factor had a tendency to be more strongly associated with visual distortions and underlying cortical hyperexcitability. Importantly, there were no significantly reliable correlations between measures of anomalous experience and the number of AVDs reported for the high-frequency baseline grating. These findings provide support for previous research (Braithwaite et al., 2013a, 2013b; Wilkins, 1995) and suggest that the propensity to experience more AVDs in response to the presentation of the medium-frequency grating, can be associated with propensity to experience certain anomalous perceptions in general. In addition, the selective effect for the medium-frequency grating suggests that these effects are not due to generic response biases that can be present in some groups of hallucinators. If this were the case then such individuals should have produced elevated scores for all gratings and under all conditions. Clearly this was not the case.

In terms of tDCS, there were no significant effects of brain-stimulation (from either excitatory or inhibitory configurations) seen for the high-frequency baseline grating. The number

of AVDs remained roughly constant across conditions. In contrast, there was a reliable effect of excitatory stimulation on the number of AVDs reported for the crucial medium-frequency grating. Indeed, the significant Stimulation x Grating interaction that occurred can be seen to be principally driven by the effects of excitatory stimulation on the medium-frequency grating alone (see Figure 2).

In addition to this, the correlation analysis based on the delta values was also particularly noteworthy and revealing. This examination showed that individuals who responded more to excitatory (anodal) tDCS stimulation of the visual cortex, tended also to respond less to inhibitory (cathodal) tDCS stimulation of the visual cortex. Again, these effects were only reliable for the medium-frequency grating (though were also present to a lesser and non-reliable degree for the high-frequency grating).

Crucially both these findings are consistent with the presence of a hyperexcitable cortex. If the cortex is hyperexcitable, then we might predict that it would be easier to stimulate and hence be more readily reactive to excitatory tDCS stimulation - possibly due to a lack of involvement from inhibitory processes. It follows that if there is a reduced efficacy in inhibitory processes, then inhibitory tDCS stimulation will also be less effective - as the deficient inhibitory neural processes cannot be engaged as effectively by inhibitory configurations of tDCS. Therefore, cortices that are easier to excite, might also be harder to inhibit - at least in some cases and for visual and visual association cortex. This was exactly what was found. Furthermore, the delta AVD values (excitation - sham) for the medium-frequency grating also correlated positively with propensity to experience anomalous perceptions - though this was larger and only significant for the TLE factor (Table 2). Those scoring high on measures of anomalous perceptions, showed a modest, though reliable, trend towards increased AVDs as a function of excitatory tDCS. One study (Batsikadze et al. 2014) has shown that high cathodal stimulation (2 mA over a 7x5 cm electrode) can actually reverse the cortical effect from inhibition to excitation (so that a similar excitatory

effect is observed following both cathodal and anodal stimulation). As the stimulation parameters used in the present study are at the higher end of tDCS protocols (though are not the same as the Bathikadze et al., 2014 study), one might speculate as to whether such effects were present in the current study.

However, such a reversal is not likely to have happened here. First, both the electrodes and the amplitudes in the Bathikadze et al. study were both increased relative to our protocol here and such conjoint increases may have multiplicative effects on stimulation. Second, other studies using a similar montage to the present study (1 or 2 mA over 5x5 cm electrodes) have shown clear inhibitory effects under higher intensity (2 mA vs 1 mA) stimulation (e.g., Galea et al., 2009). Indeed, Galea et al., (2009) directly compared 1 mA and 2 mA cathodal stimulation and found inhibitory effects only after 2 mA stimulation. So inhibitory effects have been shown for similar configurations and intensities to those used in the current study (i.e., no reversal effect).

Third, if a reversal was present, then this should have equated the effects of cathodal and anodal stimulation in the present study. Clearly, this did not happen. For example, when collapsed across all participants, there was a reliable, reduction in the number of AVDs for inhibitory relative to sham conditions - suggesting a clear suppression of visual cortex. The difference is even bigger when contrasting overall excitatory vs inhibitory effects. This is not consistent with the idea that inhibitory stimulation had been reversed as this makes the exact opposite prediction than what we actually observed. By this 'reversal' account, effects of inhibition (hence now, excitation) would predict more AVDs for cathodal (inhibitory) relative to sham, and a smaller difference between anodal and cathodal stimulation as both would essentially be excitatory under conditions of reversal.

Interestingly, our findings are also supported by studies that have examined cortical hyperexcitability in migraineurs with aura (Chadaide et al., 2007). Chadaide et al (2007) found that after 10mins of anodal stimulation, using the same stimulation sites as used here (Oz and Cz) there

was a significant reduction in phosphene thresholds - but only for the migraine with aura group. In addition, there were no effects of cathodal stimulation for this group. Again this suggests that the visual cortex responded better to excitatory stimulation and less well to inhibitory suppression - consistent with the notion that a hyperexcitable cortex underlies the experience of aura / hallucination.

The findings presented here provide a direct demonstration, that the cortex of non-clinical levels of those predisposed to certain anomalous perceptions is hyperexcitable to some degree and that such factors are present, measurable and quantifiable as a background state. Previous work from our laboratory has shown that those predisposed to certain types of hallucinations (e.g., visual out-of-body experiences / anomalous body experiences) experience more visual discomfort and more visual illusions as a result of viewing the medium-frequency grating (Braithwaite et al., 2013a, 2013b). This suggests that at least some non-clinical hallucinators do indeed display elevated levels of pattern-glare and hence, reflect greater cortical hyperexcitability relative to controls. The present findings lend further weight to these observations, by adding more objective evidence in the form of direct stimulation of the cortex via tDCS.

These findings are also consistent with 'continuum' notions of hallucination proneness (Bentall, 1990; Collerton, Perry, & McKeith, 2005; Johns & van Os., 2001; McCreery & Claridge, 2002; Lopez-Rodrigo, Paino Pineiro, Martinez Suarez, Caro, & Lemos Giraldez, 1997; Meehl, 1962; Schwartzman, Maravic, Kranczioch, & Barnes, 2008; Serper, Dill, Chang, Kot, & Elliot, 2005; van Os, Hanssen, Bijl, & Ravelli, 2000). According to this view, individuals can be placed somewhere along a continuum of predisposition to anomalous experience. In the present case this continuum refers specifically to cortical hyperexcitability as a contributing factor. It follows that individuals placed further along this continuum, reflecting increased visual cortical hyperexcitability, will thus be more predisposed to visual / multi-sensory anomalous experience. Collectively, the present study provides a novel approach for studying subtle neurocognitive biases

with the potential to inform a more comprehensive understanding of aberrant perceptual experiences in both neurological and non-neurological groups.

Limitations, implications, & Future research

The present study examined tDCS stimulation in relation to pattern-induced visual aversion, cortical hyperexcitability, and anomalous visual experiences. As very few studies have examined pattern-glare effects in non-neurological samples, the findings should be viewed as preliminary and tentative. One important limitation to acknowledge is that some of the effects reported in the present study are moderate at best. For example, correlations between questionnaire measures and effects from stimulation, while statistically significant, were not large. In addition, in real terms, excitatory tDCS stimulation induced, on average, one more AVD relative to sham conditions. There are a number of reasons for why this might be the case.

In the current protocol although participants received 20mins of brain stimulation in total, only half of this (10mins) was provided before the experiment began. It may well be the case that the full effects of tDCS could be improved if the stimulation duration was increased to maximise its impact. Increasing the duration of stimulation, and / or the intensity of it, may impact on the efficacy of tDCS in these circumstances. In addition, it should be noted that presenting a highly irritable, aversive striped pattern is itself a potent method of stimulating the visual cortex, in that such stimuli can over-stimulate neurons in the visual system (Huang, Cooper, Satana, Kaufman, & Cao, 2003; Huang et al., 2011; Wilkins, 1995; Wilkins et al., 1984). Indeed, it is this form of aberrant neuronal response that is thought to underlie the existence of visual distortions that many individuals experience as part of their symptomatology. In some cases, the visual stimulation may be too strong to further complement or subdue with tDCS. Therefore, all conditions in the current experiment can be viewed as being stimulatory in nature to some degree.

One reservation and common misunderstanding is that a hyperexcitable brain that reacts more strongly to the visual stimulation, may react less strongly to tDCS - due to some kind of pre-existing ceiling effect. According to this view, a brain that is already hyperexcitable and already producing high levels of AVDs in the sham condition, would be so near to its maximal ceiling response, that additional stimulation from tDCS could not produce observable and reliable effects on top of that which is already present. This notion might also be applied to neurological and clinical groups prone to visual aura / hallucination (i.e., migraineurs with aura, occipital epilepsy, migralepsy) who may well be nearer some absolute ceiling level as a background state.

However, a closer examinations of both the issues and findings suggest that such notions are unlikely. For example, some studies have shown that tDCS actually produces a stronger response with migraine groups, relative to controls, which goes directly against the notion of ceiling effects in this regard (Chadaide et al., 2007). In addition, in terms of the present sample there was no reliable difference between the number of AVDs between the medium and high-frequency gratings under sham conditions. This goes against the notion that absolute ceiling effects were present at least in terms of the whole sample. Furthermore, the current sample consisted of non-clinical participants who are, by definition, not predisposed to the level of anomalous perceptions and AVDs as those observed for clinical and neurological groups (i.e., migraineurs with aura / patients with epilepsy: Marcus & Soso, 1989; Wilkins, 1995; Wilkins et al., 1984). Finally, statistically reliable effects of excitatory tDCS did emerge, and increasingly so for those predisposed to anomalous perceptions. This pattern of results goes against the direction predicted by that of a ceiling account.

The reliable though mild effects of some correlations to questionnaire measures (see Table 2) may simply reflect some insensitivity in the questionnaire measures (and their subscales) themselves. The TLE factor contains a variety of items, two of which are visual in nature, and the rest reflect a variety of sensory and multi-sensory anomalies - not all of which may be directly

related to the mechanisms mediating pattern-glare. Furthermore, there is some evidence to suggest that direct experimental tests of pattern-glare are a better predictor of behavioural performance at the time of testing than questionnaires seeking to measure more general latent signs of such factors (Hollis & Allen, 2006). The present findings now provide the evidential basis for studies using a broader range of neuroscientific methods and tasks (i.e., visually evoked potentials / neuroimaging), to provide further direct investigations of the nature of cortical hyperexcitability and anomalous perception in non-clinical as well as neurological / clinical groups.

In summary, in the current study, the presence of cortical hyperexcitability was evidenced by (i) reports of visual distortions induced by a computerised pattern-glare task; (ii) cortical responsivity to excitatory tDCS brain stimulation; (iii) questionnaire measures of predisposition to specific anomalous perceptions, and (iv) associations between all these factors. Collectively, the present findings add more direct support to the view that elevated cortical hyperexcitability is implicated in predisposition to anomalous experience even in some non-clinical groups. In addition to this, the present findings also suggest that the pattern-glare task does index, at least in part, cortically mediated hyperexcitability.

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Table 1. Descriptive statistics for measures of proneness to anomalous perceptions from the current study (n = 60)

	Mean	Median	Range	SD
CAPS	4.1	3.0	12	3.16
TLE Factor	3.1	3.0	8	2.18

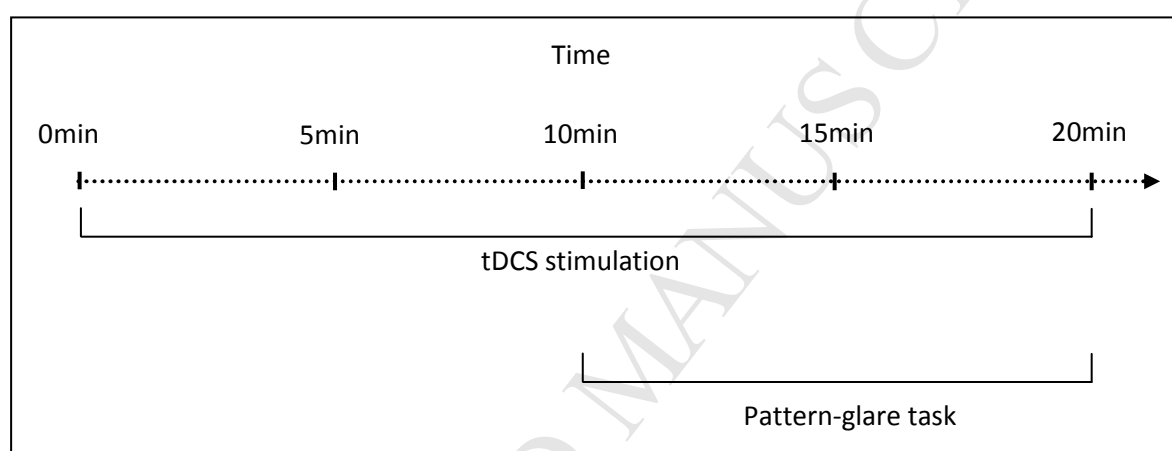


Figure 1. A schematic illustration of the time-line for the current study. For the stimulatory conditions (anodal and cathodal), the pattern-glare task started after 10mins of tDCS stimulation, and continued for a further 10mins. tDCS stimulation ceased at the end of the pattern-glare task, resulting in 20mins of stimulation in total.

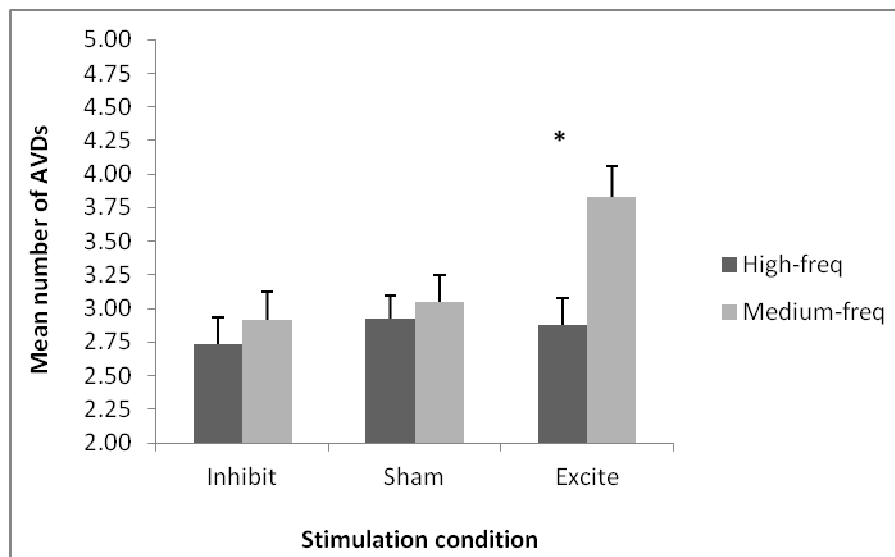


Figure 2. Mean number of AVDs as a function of grating (High / Medium) and tDCS brain-stimulatory condition (Inhibit / Sham / Excite). Error bars = 1 Standard error. Asterix denotes significant differences.

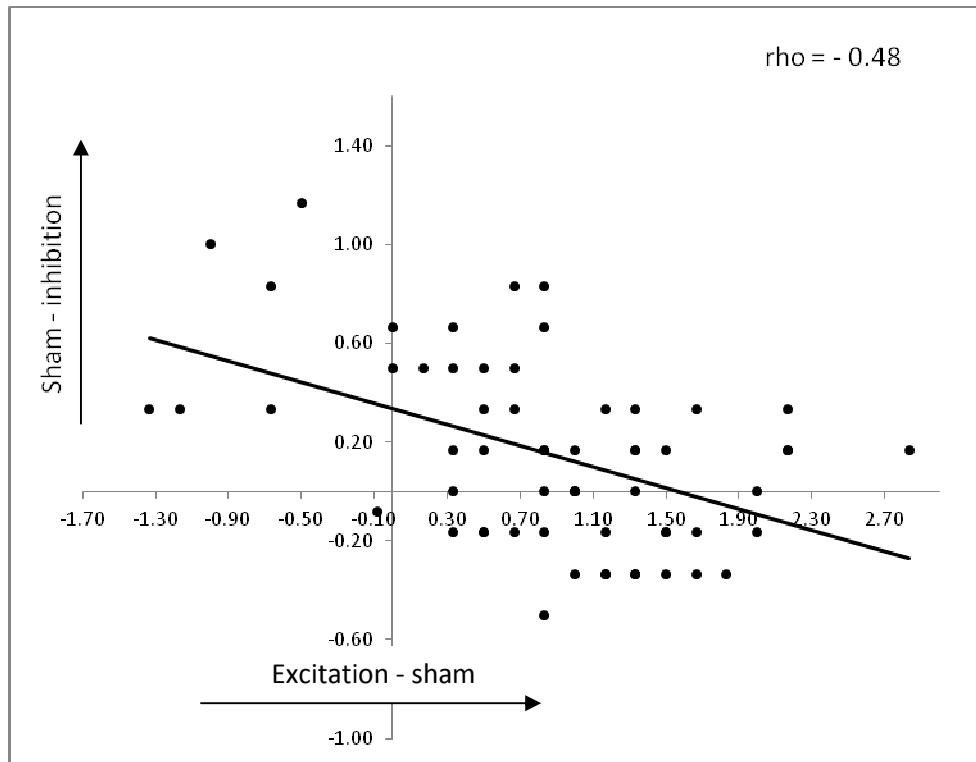


Figure 3. Scatterplot for the medium-frequency grating which was the only one to have produced a significant negative correlation. The x-axis shows the subtractions from the AVDs from the excitatory configuration of tDCS minus the AVDs from the sham condition (as an index of excitation). The y-axis shows the subtractions between the AVDs from the sham condition minus the inhibitory configuration of tDCS (as a measure of inhibition). Note, as the efficacy of excitation increases, the efficacy of inhibition decreases. Both findings are consistent with the presence of increased cortical hyperexcitability (see General Discussion).

Table 2. Correlation coefficients and p-values for both the CAPS / TLE measures and the number of AVDs reported after subtraction for the medium-frequency grating (* denotes significant at $p=.05$).

	Coefficient	p-value
CAPS x Excite - sham	0.18	= .18
CAPS x Sham - inhibit	-0.02	= .87
TLE x Excite - sham	0.29*	= .02*
TLE x Sham - inhibit	-0.07	= .62